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13. ABSTRACT (Maximum 200 Words) Magnetic resonance imaging (MRI) techniques have the potential to greatly improve breast cancer detection, diagnosis, and treatment. Contrast-enhanced breast MRI has shown greater sensitivity than mammography in the detection of small breast lesions, and can also successfully image dense, augmented, and postoperative breasts. MRI is becoming a valuable tool in surgical planning and is additionally being investigated for monitoring tumor response to therapy. The purpose of this study is to develop and optimize new diagnostic models for improved discrimination of benign and malignant breast tissue. It is hypothesized that the addition of dynamic enhancement data from muscle and vessels to models which currently utilize only lesion enhancement information will improve tumor differentiation and will minimize patient to patient variations to improve the overall specificity of MRI in the detection of breast cancer. Breast MRI data acquisition techniques will be modified and patient data analyzed to provide optimal dynamic behavior information of the tissues. The performance of the resulting models will be evaluated and the increase in MRI specificity due to the application of optimized models will be quantified. The outcome of this work will contribute to the development of an accurate method of assessing tumor treatment response using MRI.				
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INTRODUCTION

Breast cancer is the most common malignancy of women in the United States, and is the second leading cause of cancer death in American women. Contrast-enhanced breast MRI has shown greater sensitivity than mammography in the detection of small breast lesions, detecting tumors at sizes less than 1cm, and can also successfully image the dense breast (1-5). Additionally, MRI is a valuable tool in surgical planning for lumpectomy, can be used for monitoring tumor response to therapy, and has demonstrated usefulness in distinguishing scar tissue from recurrent breast carcinoma (6-8). New models which accurately describe tissue characteristics such as tumor grade, size, histologic type, extent of angiogenesis or microvessel density, etc. using breast MRI would be valuable predictive tools in the diagnosis and treatment of breast cancer (9).

The purpose of this study is to develop and optimize new diagnostic models for improved differentiation between benign and malignant breast tissue and enable accurate characterization of tumor extent and aggressiveness of breast cancer using MRI. It is hypothesized that the addition of dynamic enhancement data from muscle and vessels to models which currently utilize only lesion enhancement information will improve tumor differentiation and will minimize patient to patient variations to improve the overall specificity of MRI in the detection of breast cancer. Breast MRI data acquisition techniques will be modified and patient data will be analyzed to provide optimal dynamic behavior information of the tissues. The performance of the resulting models will be evaluated and the increase in MRI specificity due to the application of optimized models will be quantified. This research will contribute to the overall development of a high resolution 3D imaging method for staging of breast cancer, and applications of the resulting models will ultimately facilitate the transition of breast MRI from a research tool to a clinically useful technique.

BODY

Technical Objective 1: Development of MRI Data Acquisition Techniques

MRI Acquisition Sequences. The contrast-enhanced MRI data acquisition sequence was formalized corresponding to our temporal and spatial resolution requirements. We worked to maximize the temporal resolution of the data acquired for increased dynamic enhancement information of the tissues while still maintaining high spatial resolution to adequately identify tumor extent. While we originally expected to reduce our scan time considerably, we found that this was not feasible with current limitations. We have requirements on our contrast-enhanced imaging sequence which include full breast coverage, fat suppression, and high spatial resolution. Working with these restraints and our current hardware limitations, we were able to reduce our scan time from 5.6 minutes to 5.0 minutes per acquisition without sacrificing image quality.

Additionally, a new diffusion-weighted MR sequence is being investigated for usefulness in identifying breast cancer. MRI non-invasively measures the apparent diffusion coefficient (ADC) of water, which is sensitive to the biophysical characteristics of tissue. Previous work has shown that ADC values in the brain are significantly different for tumor and normal tissue (10), and significant differences ($p < 0.01$) were found between the ADC values for malignant masses, benign masses, and cysts in the liver (11). Diffusion-weighted imaging of breast cancer tumors implanted in mice has been successful at differentiating viable tumor cells from necrosis and fibrosis, and detecting early treatment response within tumors (12-14). A recent study was able to obtain reproducible measurements of diffusion coefficients of breast tissue in vivo in human volunteers using diffusion-weighted MRI (15). Preliminary findings from this group also demonstrate differences in the ADC values for normal breast tissue, cancer, and cysts, indicating the potential for using diffusion imaging to improve the specificity of breast MR and for classifying breast lesions. Additional advantages of diffusion imaging are the short scan times, taking less than a minute per scan, and the fact that no contrast injection is needed for this type of imaging. We are adapting an existing sequence for use in the breast and it will be incorporated into the breast MR exams following the contrast-enhanced acquisitions. Studies will be conducted to determine the value which diffusion measurements provide to diagnostic models for characterizing breast cancer.

Although it was originally proposed that preliminary testing on animals would be an efficient method for developing new acquisition sequences, we have not found this to be true. Many logistical problems have made it difficult to directly translate from imaging animals to humans on our clinical scanner. These issues include the small size of the animals necessitating use of a different receiver coil, faster heart and breathing rates affecting image quality and enhancement rates, and difficulty of achieving controlled contrast injections in the mice. In conclusion, we feel that the ample number of human volunteers available at our center renders the animal studies unnecessary for this work.

Analysis Software. The MR images are evaluated on a Sun Ultra 1/170E workstation (Sun Microsystems, Mountain View, CA). All image analysis software was created with

IDL (Interactive Data Language, Research Systems, Boulder, CO). Many new functions have been incorporated into the previously developed analysis software. To accommodate different scanning techniques, the software was adapted to allow measurements to be taken from more than three time points. The software now allows the user to manually register images from any of the multiple time points to adjust for patient motion between acquisitions. The user can draw an ROI on one time point, and measurements will automatically be taken from corresponding locations in all time points. This data can be recorded by writing to a file for further analysis or can be displayed on a plot in order to view changes with time.

In addition, new methods were developed for taking accurate measurements in vessels. It was found that the relatively small size of most vessels in the breast makes it difficult to draw an ROI contained within a vessel, and also that most vessels are virtually invisible on our precontrast T1-weighted images, making it difficult to obtain a reliable precontrast vessel measurement. The new technique requires the user to draw an ROI on the vessel of interest on the post-contrast maximum intensity projection (MIP), where the projection of the vessel is much larger than it would be in a single sagittal image. The software then uses the pixels from the same locations for taking ROI measurements from the precontrast and other postcontrast scans.

Another exciting area of development with the software is the addition of a semiautomated volumetric analysis algorithm. Current major problems associated with breast MRI are the large amount of image data, the time-intensive analysis required, and varying reproducibility of measurements (16,17). By automating the technique, we feel the analysis of patient exams can be performed in a more timely and reproducible manner, and thus improve the clinical utility of breast MRI. Total analysis time for a patient study was reduced from 30-45 minutes for the manual analysis to approximately 5 minutes using the new semiautomated technique (18). This new method is designed to gather the same measurements from breast MRI studies which are currently collected manually, and in addition allows many new volumetric quantifications to be made to better characterize the lesions. We feel these MRI measurements may provide a powerful quantitative method to non-invasively measure changes in tumor volume and biologic activity over the course of treatment. Studies are underway to assess the performance of the new semiautomated analysis technique as compared to the manual technique and to investigate the value of the volumetric measurements for identifying treatment response in tumors (19). See appended abstracts for more details of the automated software.

Patient Database. A spreadsheet was initially created using Microsoft Excel (Microsoft Corporation, Redmond, WA) to organize patient data for developing diagnostic models. Information contained in the spreadsheet included measurements at each time point from enhancing lesions, vessels, and muscle, and pathology diagnosis of the lesions for each patient. Eventually this data was incorporated into a larger database containing all patient data, compiled from treatment, clinical, surgical and histological assessments, as well as MR. The larger database was developed using a FileMaker Pro (FileMaker, Inc., Santa Clara, CA), and statistical analysis of particular parameters is currently done using Excel spreadsheets with data downloaded from the larger database.

Technical Objective 2: Optimization of MRI diagnostic specificity

Patient MR Exams. Many patient exams have been processed using the new software to measure enhancement in lesion, muscle, and vessels and all measurements and calculations are recorded in the patient database. All appropriate older studies stored on optical disks were analyzed, and new studies have been systematically processed after each patient is scanned. Patients included in the study are those who are imaged prior to undergoing surgery. Subsequent pathology reports are used as the gold standard for comparison with MRI results. Data for over 100 patients has been analyzed to date for this study. New patient studies are currently being acquired and more than 200 exams total will be completed in the next year.

Diagnostic Models. Once sufficient patient data is collected, the next step is to develop new diagnostic models for characterizing enhancing regions of breast MRI images. Our initial attempts to introduce improved specificity into our imaging technique included the use of the signal enhancement ratio (SER) index, which compares early to late enhancement behavior in the tissue. SERs have shown promising results for quantifying tumor aggressiveness and differentiating between benign and malignant lesions (20-22). We feel that incorporating other factors such as the response of nearby muscle or vessels in the breast could help to increase the accuracy with which the models can characterize breast lesions. Normalization of enhancement ratios of breast tissue with that of normal muscle tissue could help reduce inconsistencies between patients due to variances in delivery of contrast agent and differences in circulation of contrast in the body. Additionally, normalization of enhancement ratios of breast tissue with that of blood vessels in the breast may help reduce effects of variances in circulation and differences in contrast delivery between patients as well.

Initial investigations have been made to ascertain the best performing model using measurements from the three time points acquired in the contrast-enhanced scan for each patient. Initial investigations of using muscle and vessel signal changes to normalize enhancement curves have not significantly improved specificity in these analyses (23). Further attempts will be made using a larger data set.

Thresholds and cutoffs for calculations must be further optimized to minimize effects of noise and to improve discrimination between benign and malignant tissue. ROC curve analysis will be helpful in determining these parameters for best results. It has been suggested that for patients who have recently completed chemotherapy, MR contrast enhancement rates and levels are affected and may necessitate a different set of criteria for evaluation(24). In future work, we will assess this problem.

In addition, diffusion coefficient maps will be generated from the new DW-MRI acquisitions. Measurements will be taken from normal tissue and in breast tumors, and statistical analysis will be used to determine the value of DW-MRI for identifying and characterizing tumors in the breast.

KEY RESEARCH ACCOMPLISHMENTS

- Developed a new semiautomated software technique to increase the efficiency of analysis of breast MR exams and to help characterize volumetric parameters as well as dynamic response of breast lesions.
- Formalized MR acquisition sequence and collected measurements from over 100 patient MR exams for development and testing of diagnostic models.
- Proposed and tested some initial models incorporating dynamic enhancement data in lesions and assessed the effect of normalizing models with measurements from corresponding vessels and muscles.

REPORTABLE OUTCOMES

1. Partridge S, Heumann E, Hylton N. Semi-automated analysis for MRI of breast tumors. *Studies in Health Technology and Informatics*, 1999; 62:259-60.
2. Partridge S, Esserman L, Heumann E, Tripathy D, Hylton N. Validation of a semi-automated breast MRI analysis technique for tumor diagnosis and evaluation of response to therapy. *Proceedings of the ISMRM 7th Scientific Meeting*, May 1999; 3:2170.
3. Hylton NM, Esserman LJ, Partridge SC, et al. Clinical Evaluation of a three-time point breast MRI method. *Proceedings of ISMRM 6th Scientific Meeting*, April 1998; 2:933.
4. Partridge SC, Hylton NM, Wang WL. A comparison of analytical models for improved discrimination of benign and malignant breast tissue. *Proceedings of ISMRM 6th Scientific Meeting*, April 1998; 2:934.

CONCLUSIONS

Thus far, we are on track and meeting the schedule for the first 12 months provided in our initial proposal. A versatile software tool has been developed for enabling all necessary measurements to be taken from the patient studies. In addition, a semiautomated algorithm has been incorporated into the software to increase the efficiency of analysis and to help characterize volumetric parameters as well as dynamic response of breast lesions. Initial data from contrast-enhanced scans has been used to begin developing diagnostic models that incorporate normalization with vessel and muscle measurements. Diffusion MRI is also being examined and may provide valuable insight to biologic activity in the tissue, which can ultimately improve diagnostic models.

In the following year, we will focus more on refinement of the diagnostic models using measurements from the contrast-enhanced and diffusion MRI scans. Models will be trained for optimum differentiation of benign and malignant tissue in the breast by adjusting corresponding thresholds and cutoffs.

We feel that the next step for the outcome of this work lies in assessing treatment response for neoadjuvant chemotherapy. Contrast-MRI may provide a powerful quantitative method to non-invasively measure changes in tumor volume and biologic activity over the course of treatment, but this will depend on the development of analytical methods that are accurate, efficient, and not subject to operator variability. Such a methodology could greatly aid in the evaluation of new treatment strategies in clinical trials by offering a more accurate method of assessing tumor response than is currently available using mammography, ultrasound, and clinical exam.

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APPENDICES

Semi-Automated Analysis for MRI of Breast Tumors

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Magnetic resonance imaging (MRI) techniques have the potential to greatly improve breast cancer detection, diagnosis, and treatment. Currently, a major problem associated with breast MRI is the overwhelming amount of data acquired during an exam, and the time-intensive analysis required to evaluate the images. We have developed a software platform for semi-automated analysis to assess both the tumor extent and overall grade or severity based on our diagnostic criteria. In a test subset of over 50 patients, the automated program produced results more accurate overall than those measurements taken manually, with a reduction in time for analysis from approximately 45 minutes down to 5 minutes per patient study.

1. Introduction and Purpose

Breast cancer is the most common malignancy and the second leading cause of cancer death among American women. Although mammography is currently the most common detection method, contrast-enhanced breast MRI has shown greater sensitivity than mammography in the detection of small breast lesions, and can also successfully image dense, augmented, and postoperative breasts.[1,2] Additionally, MRI is becoming a valuable tool in surgical planning for lumpectomy and can be used for monitoring tumor response to therapy.[3]

Diagnostic techniques for breast MRI involve assessing both the morphology and the pattern of contrast enhancement kinetics; a number of recent publications have proposed diagnostic models incorporating these features.[4,5] Due to the large amount of data acquired, these diagnostic assessments are time-intensive and typically take more than 30 minutes to evaluate a single breast MRI exam. In addition, a skilled operator must perform the analysis and interoperator variability may affect the reproducibility of the results.

The purpose of this study was to design a semi-automated method for evaluation of breast MRI exams which would produce a diagnostic assessment including lesion extent, diagnosis, and tumor characterization. By automating the technique, analysis of patient exams can potentially be performed in a more timely and reproducible manner.

2. Methods

The MR images are evaluated on a Sun Ultra 1/170E workstation (Sun Microsystems, Mountain View, CA). The analysis software platform was developed using the Interactive Data Language (IDL, Research Systems, Boulder, CO) programming environment. The diagnostic model we currently use at our institution is the signal enhancement ratio (SER) index for suspicious enhancing lesions which compares early to late enhancement behavior in the tissue and has shown promising results for quantifying tumor aggressiveness and differentiating between benign and malignant lesions. [6]

The manual analysis technique requires the user to browse through the images of corresponding locations at different times after injection to take measurements and determine lesion extent. The user searches for the highest SER value in the lesion by manually drawing regions of interest (ROIs) for which signal intensities and SERs are calculated. The new semi-automated technique reduces the number of images a user must view by first generating maximum intensity projections (MIPs) in three orthogonal directions from the

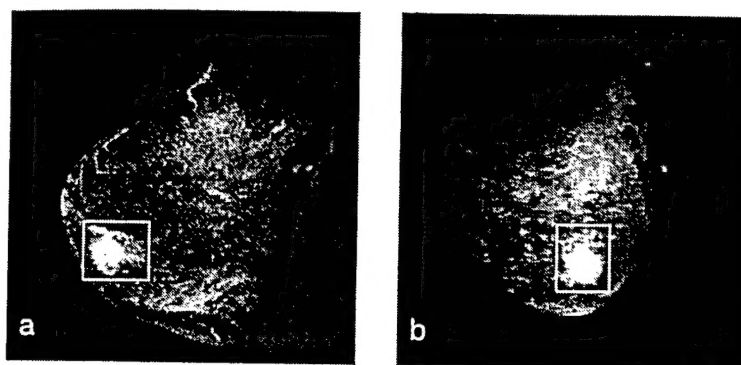


Figure 1. MIPs of MR images of the entire breast acquired 3 minutes post-contrast injection. a) Latero-medial, and b) Cranio-caudal with user-defined boxes indicating volume to be evaluated.

data for each time point. This condenses the information from 180 images to a set of 9 images, which allows the user to more quickly evaluate the extent of the lesion. (Figure 1) Next, the user draws a box around the lesion (Figure 1b) on two orthogonal projections, defining a restricted volume to be evaluated. The software calculates SER values for all voxels within the defined volume and identifies the peak SER as the ROI (>5 contiguous voxels) with the highest mean SER value. Tumor volume is then calculated by summing voxels within the region which meet tumor enhancement criteria. The pattern of enhancement is also characterized by identifying the proportion of voxels with high, moderate or low SER values.

3. Results and Conclusions

Fifty-seven patients with suspicious mammographic or clinical findings were scanned prior to undergoing surgery. The diagnostic results of benign or malignant from the analysis using both techniques were compared to histopathology reports. The pathologies included 13 benign and 44 malignant (including 8 non-invasive malignancies) cases. The semi-automated analysis was equally as accurate as the manual technique, with both methods correctly diagnosing 48 cases in 57 and achieving sensitivities of 93% and specificities of 57%. A reduction in time for analysis was observed from approximately 45 minutes for the manual method to 5 minutes for the semi-automated method. While reproducibility studies have not yet been performed, our feeling is that the reproducibility is much higher for the semi-automated technique since the only interaction by the user is to define the boundaries of the restricted volume in order to include the entire lesion.

The new semi-automated technique allows analysis to be done more quickly and with less training for accurate and potentially more reproducible results. This improvement in efficiency will ultimately facilitate the transition of breast MRI from a research tool to a clinically useful technique.

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Validation of a Semi-Automated Breast MRI Analysis Technique for Tumor Diagnosis and Evaluation of Response to Therapy

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Purpose

The purpose of this study was to validate a semi-automated method for lesion diagnosis and evaluation of lesion extent and enhancement kinetics.

Introduction

Contrast-MRI may provide a powerful quantitative method to non-invasively measure changes in tumor volume and biologic activity over the course of treatment, but this will depend on the development of analytical methods that are accurate, efficient, and not subject to operator variability. Such a methodology could greatly aid in the evaluation of new treatment strategies in clinical trials by offering a more accurate method of assessing tumor response than is currently available using mammography, ultrasound, and clinical exam.

Current major problems associated with breast MRI are the large amount of image data, the time-intensive analysis required, and varying reproducibility of measurements.[1,2] By automating the technique, analysis of patient exams can potentially be performed in a more timely and reproducible manner and thus improve the clinical utility of breast MRI.

Methods

56 patients with suspicious mammographic or clinical findings were imaged prior to undergoing surgery. Subsequent pathology reports for each patient were compiled and information on lesion grade, size, and histologic type (benign, ductal carcinoma in situ (DCIS), invasive, etc.) were recorded for comparison with the results of manual and semi-automated image analyses.

All patients were imaged using a fat-suppressed 3D-FGRE sequence, TR/TE=11.2/4.2ms, 2 NEX, 18cm FOV, sixty 2mm thick slices, 256x192 matrix, on a 1.5 T GE Signa EchoSpeed imager using a dedicated breast receiver. Three imaging sequences were acquired, one before contrast injection (Time 0) and two consecutively after (Time 1 and Time 2, centered around 2.8 minutes and 8.1 minutes respectively after injection of 0.1mmol/kg body-weight Gd-DTPA).

All image analysis software was created with IDL (Interactive Data Language, Research Systems, Boulder, CO). Manual MR image analysis consisted of defining regions of interest (ROIs) inside suspected lesions for which average signal intensities are then calculated at each time point (S0, S1, S2). The diagnostic model used is the signal enhancement ratio (SER) index for suspicious enhancing lesions which compares early to late enhancement behavior in the tissue and is calculated by $(S1-S0)/(S2-S0)$. SERs have previously shown promising results for quantifying tumor aggressiveness and differentiating between benign and malignant lesions. [3] The user found the highest SER value by choosing ROIs at various locations in the lesion, and determined lesion extent by measuring it at its widest points.

In the semi-automated technique, the user defines a restricted volume by drawing a box around the lesion on two orthogonal maximum intensity projection (MIP) views created from the Time 1 images. (Fig. 1) The software calculates SER values for all voxels within the defined volume with enhancement >80% and identifies the peak SER as the ROI (>5 contiguous voxels) with the highest mean SER value. Tumor volume is then calculated by summing all voxels with appropriate SER (>1.0), and the pattern of enhancement is characterized by identifying the fraction of tumor with high, moderate or low SER values. The user is given

the opportunity to reject the initial automated ROI selection if it is found to be improperly chosen inside a vessel. This analysis method is limited by misregistration due to patient motion.

To investigate whether this method is useful in quantifying response to treatment, and in particular identifying early response, measurements were taken of 31 invasive lesions in 24 patients undergoing neoadjuvant chemotherapy. In addition to changes in tumor volume and peak SER value for the lesion, we also quantified changes in the fractions of the lesion with high and low SER values.

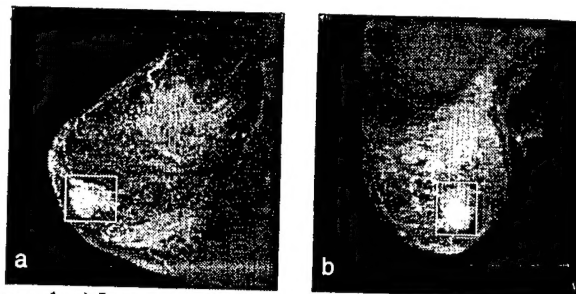


Figure 1. a) Latero-medial, and b) Cranio-caudal MIPs with user-defined boxes indicating volume to be evaluated.

Results

The diagnostic value of both analysis techniques was tested against proven patient diagnosis as determined by pathology. In a group of 56 lesions (consisting of 12 benign, 7 DCIS, and 37 invasive pathologies) evaluated, the semi-automated program produced results equally as accurate as measurements taken manually. Both analysis techniques independently produced sensitivities of 93% and specificities of 50%. (Note: This image analysis did not incorporate morphologic features which have been shown to increase diagnostic specificity. [4]) An overall reduction in time for the quantitative analysis was observed from approximately 45 minutes down to 5 minutes per patient study using the semi-automated technique, with a marked observed improvement in the reproducibility of the measurements.

In the group of patients receiving neoadjuvant chemotherapy, we found that changes in tumor volume correlated well with clinical and pathologic assessment of tumor response. The significance of SER changes over the course of treatment has not yet been established, however in continuing studies we are investigating whether SER response in combination with volumetric response is predictive of patient outcome.

Discussion

The new semi-automated technique allows analysis to be done more quickly and with less training for accurate and potentially more reproducible results. This improvement in efficiency will ultimately facilitate the transition of breast MRI from a research tool to a clinically useful technique.

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A Comparison of Analytical Models for Improved Discrimination of Benign and Malignant Breast Tissue

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Introduction:

Breast MRI techniques have the potential to greatly improve breast cancer detection, diagnosis, and treatment. Our imaging technique was designed primarily for presurgical staging of disease extent and therefore a priority was placed on achieving high resolution images with relatively low temporal resolution. In order to improve specificity, we acquired an additional post contrast time point. The purpose of this study was to investigate analytic models for improved differentiation between benign and malignant breast tissue and enable accurate characterization of tumor extent and aggressiveness using contrast-enhanced breast MRI.

Methods:

The majority of our patient population have confirmed malignancies as determined by biopsy or fine needle aspiration (FNA). Over one hundred patients were imaged prior to undergoing a surgical procedure. All patients were imaged using a fat-suppressed 3D-FGRE sequence, TR=11.2ms, TE=4.2ms, 2 NEX, 18-20cm FOV, 256x192 matrix, on a 1.5 T GE Signa Echospide imager using dedicated breast coils, resulting in 60 2mm thick sections with in-plane resolution of 0.6-0.8mm and scan time of 5.4 minutes. Three imaging sequences were acquired, one before contrast injection (Time 0) and two consecutively after (Time 1 and Time 2, centered around 2.8 minutes and 8.1 minutes after contrast injection, respectively). Using a software tool developed with IDL (Interactive Data Language) to analyze the images, regions of interest (ROIs) were defined inside vessels, chest muscle, and suspected lesions. Average signal intensities were calculated for these regions at each time point (S0, S1, S2 for lesions, M0, M1, and M2 for muscle, and V0, V1, and V2 for vessels). Figure 1 illustrates a typical ROI defined for an enhancing lesion and corresponding images obtained at each time point. Registration problems resulting from patient motion between the three scans was minimized using interactive registration tools incorporated in the software. Pathology reports from biopsy, FNA, or surgery for each patient were compiled and information on the lesion grade, size, and histologic type (benign, ductal carcinoma in situ (DCIS), invasive, etc.) were recorded for evaluation of the models. Several models incorporating the dynamic enhancement response of the breast tissue were evaluated for their ability to better discriminate between different pathologies.

Results:

The diagnostic value of each of the proposed models was tested against proven patient diagnosis as determined by pathology. The significance of the discrimination was evaluated by the Student-Newman-Keuls test for multiple comparisons. It was hypothesized that the addition of enhancement data from muscle and vessels to the models would improve tumor differentiation and reduce inconsistencies between patients due to variances in delivery of contrast agent and differences in circulation of contrast in the body. Two models incorporating muscle and vessel information were tested. One of the best performing models for separating benign from malignant was a signal enhancement ratio (SER), which compares early to late enhancement behavior in the tissue and is calculated by $(S1-S0)/(S2-S0)$. SERs showed statistically significant results ($p<.05$) for differentiating between benign and malignant lesions. Benign lesions tend to have lower SERs, with average

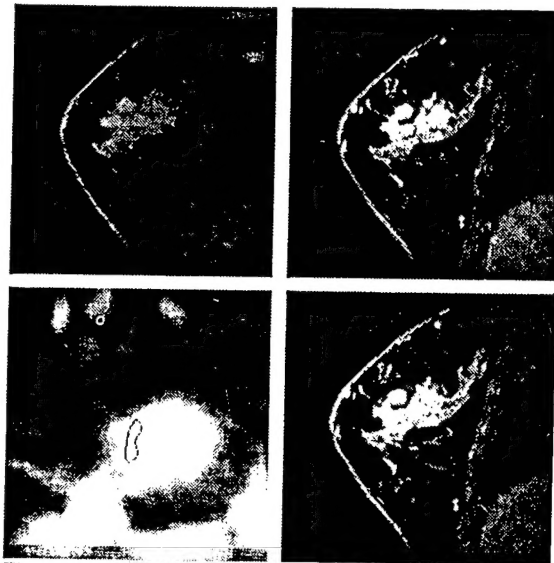


Figure 1. Clockwise from upper left: Time 0 sagittal image of breast, before contrast is injected (S0), Time 1 image at 2.8 minutes after injection (S1), and Time 2 image 8.1 minutes after injection (S2), typical ROI as defined in lesion on Time 1 image (zoom factor of 8).

SERs increasing with tumor grade. This response is believed to be a function of tumor vascularization. While the SER indexes show strong differences between benign and malignant tissue, they only marginally discriminate between the types and grades of tumors. Other models evaluated demonstrated statistically significant differences between the different grades of tumor and DCIS. A model of SER/PE where PE is the percent enhancement of the Time 1 post contrast image successfully differentiated between high grade tumors and all other pathologies including benign, DCIS and lower grade malignancies. This is a potentially important discrimination for treatment planning. In addition a model of relative washout of the contrast in the tissue calculated by $(S1-S2)/S0$ was able to further differentiate between moderate grade malignancies and high grade comedo-type DCIS and also between low grade non-comedo DCIS and benign tissue to a significance of $p<.05$. Initial investigations of using muscle and vessel signal changes to normalize enhancement curves, using models such as did not significantly improve specificity in these analysis.

Conclusions:

SERs showed promising results for quantifying tumor aggressiveness and differentiating between benign and malignant lesions. Other models were able to better discriminate tumor grades than were SERs and even showed promise at differentiating benign from low grade DCIS and malignant from higher grade comedo-type DCIS. Future work will focus on exploring the addition of morphological information to the models, further testing of utilizing muscle and vessel information, and investigating differences between pathology classifications such as ductal, lobular, and various benign pathologies to better characterize the disease.

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Clinical Evaluation of a Three-Time Point Breast MRI Method

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Introduction

MRI is proving to be effective as an adjunct procedure to mammography for evaluation of the symptomatic breast. We present the results of a clinical evaluation of 203 patients using a high resolution 3D imaging and analysis method.

Methods

Our interest in using breast MRI for pre-operative staging motivated the development of a high resolution, fat-suppressed 3D method to demonstrate the extent of disease in a single symptomatic breast. To better characterize tumor heterogeneity and increase the specificity of this method, we used a second post-contrast scan to evaluate contrast washout. Contrast enhancement was characterized using the signal enhancement ratio (SER) which compares enhancement behavior at two key points in the uptake curve; near the peak and at a delayed time point when fibroglandular tissue has enhanced significantly and some washout has occurred.

203 patients were enrolled over the period between February 1994 and November 1997. Subject age ranged from 27 to 76 years with an average age of 50 years. The subject population consisted primarily of women with a confirmed diagnosis of breast cancer on the basis of fine needle aspiration (FNA), core or surgical biopsy, or failed excision (n=111). A subset of women were evaluated for diagnostic purposes and included women with mammographic or clinical abnormalities recommended for biopsy (n=61). Other reasons for referral included patients with axillary metastasis and an unknown primary (n=7), suspicion of recurrence (n=11), high risk screening (N=4), and follow-up of previous MR findings (n=20).

We previously described the triple acquisition rapid gradient echo technique (TARGET), which is a high resolution technique designed for local staging in symptomatic women¹. TARGET consists of one precontrast (S_0) and two post contrast (S_1 and S_2) acquisitions of a fat-suppressed 3D sequence; TR = 11 ms, TE = 4.2 ms, flip angle 20°, FOV = 16-20 cm, slice thickness = 1-2 mm, imaging matrix = 256x192, oversampling to remove phase wrap (2 NEX), scan time 5.4 minutes. Fat-suppression is accomplished using a spectrally-selective inversion recovery pre-pulse². The temporal sampling was 0, 2.8 and 8.1 minutes. Image analysis was performed as follows: Breast tissue showing greater than 80 percent signal enhancement (PE) in the S_1 image was considered suspicious for malignancy. Contrast enhancement was further analyzed in suspicious tissue by computing the signal enhancement ratio (SER) = $(S_1 - S_0) / (S_2 - S_0)$.

Diagnostic specificity was calculated based on a 2x2 table using a criteria of PE > 80% as the condition for MR malignancy and pathologic diagnosis as the gold

standard. This was compared to the diagnostic specificity using the combined criteria: PE > 80% and SER > 1.2.

Results

Pathology results were available for 157 patients. Pathology findings were unavailable for 46 patients and include those who underwent neoadjuvant chemotherapy, have not yet had surgery or who chose to have surgery elsewhere. Of the 157 patients with pathology, 54 had benign findings and 103 had malignant findings. When PE > 80% was used as the sole criteria for malignancy, we found diagnostic sensitivity and specificity to be 98% and 36%, respectively. By increasing this criteria to PE > 90%, specificity increased to 46% with a decrease in sensitivity to 94%. When we used the combined criteria, PE > 80% and SER > 1.2, we found sensitivity and specificity values of 94% and 79%, respectively.

Discussion

By reducing the temporal sampling to only three appropriately chosen time points, scan time constraints can be relaxed and high resolution imaging can be used to demonstrate heterogeneity in both tumor anatomy and enhancement behavior. The three time points used in the TARGET technique were a consequence of the timing of successive 5.4 minute data acquisitions and were not optimized for specificity. Degani et. al. also proposed a three-time point method and found optimal time points to be 0, 3.5 and 12 minutes using a dose of 0.08 mmol/kg Gd-DTPA, in mouse models and human breast carcinoma³. TARGET, or a similar three-point 3D imaging method, can be easily implemented on most commercial scanners. The SER index provides a simple way to quantify and convey the enhancement behavior of tumors, leading to greater specificity.

Conclusions

The additional signal intensity information provided by a second post-contrast data acquisition, can substantially improve the specificity of a 'static' high resolution breast MRI method. Using a criteria of SER > 1.2 to identify high likelihood of malignancy, we realized a 33% improvement in specificity, with equals or exceeds values reported using dynamic techniques, without a loss of sensitivity. A three-time point method such as TARGET, combines the high specificity of dynamic techniques with the sensitivity of high resolution imaging and offers complete breast evaluation in a single exam.

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